## II. REMARKS

### Preliminary Remarks

Paragraphs of the specification that refer to specific primers or polypeptide-encoding DNA sequences are amended to identify the corresponding SEQ ID NOs.

Claim 52 is canceled, claims 38-50 and 51-54 are amended, and new claims 55-62 are added.

Claims 38, 43-45, and 47 are amended to recite that the claimed method inhibits production of IgE in a human subject with an IgE-mediated allergic disorder, support for which is found in the specification, for example, in lines 1-3 of page 76, and in Example 3 on page 80.

Claims 38 and 47 are further amended to recite that the claimed method comprises parenteral administration of an anti-human CD23 antibody comprising a human gamma-1 constant region, which antibody competes for binding to CD23 with an antibody comprising the CDRs of antibody 5E8 or antibody 6G5. Support for parenteral administration is found in the specification, for example, in lines 10-15 on page 85, and in original claims 51 and 52. Support for practicing the claimed method with an anti-human CD23 antibody that competes for binding to CD23 with an antibody comprising the CDRs of antibody 5E8 or 6G5 is found in the specification, for example, in lines 19-21 of page 21; and further on pages 24-26, which describe methods for making anti-human CD23 monoclonal antibodies, on pages on pages 45-70, which describe making antibodies having the CDRs of the 5E8 and 6G5 antibodies, and on pages 36-41, which describe a screening assay that identifies antibodies that compete with the 5E8 and 6G5 antibodies for binding to CD23.

Claims 39 and 41 are amended by replacing the recitation of a *primate or rodent antigen binding portion* with recitation of an *antigen binding portion of a primate or rodent anti-human CD23 antibody*, respectively, as suggested in the Office Action (bottom of page 4).

Amended claims 46 and 49 are directed to a method in which the anti-human CD23 antibody that is administered is an antibody having the CDRs of antibody 5E8 or antibody 6G5, support for which is found in the specification, for example, in original claim 39, and on

pages 45-70 and 75, which describe methods for cloning DNA sequences encoding the variable regions of the antibodies and expressing these using vectors containing DNA sequences encoding human constant regions, to produce chimeric, Primatized® antibodies having the variable regions of 5E8 and 6G5 and a human gamma-1 constant region. New claims 55 and 56 are separately directed to the method using antibodies comprising the two sets of polypeptide sequences recited in original claim 46.

Amended claim 48 is directed to a method in which the anti-human CD23 antibody that is administered is selected from the group consisting of a human gamma-1 antibody, an antibody comprising an antigen-binding portion of a rodent anti-human CD23 antibody, and an antibody comprising an antigen-binding portion of a primate anti-human CD23 antibody, support for which is found in the specification, for example, in original claims 39-41 and 49. New claims 60 and 61 are separately directed to the method using antibodies comprising the two sets of polypeptide sequences recited in original claim 48.

**Patentability Remarks**

35 U.S.C. §112, First Paragraph

A. Written description

Claims 38-54 were rejected under 35 U.S.C. 112, 1st paragraph, for lack of written description of claimed subject matter.

(1) The claims were rejected for lack of description of an anti-CD23 antibody comprising a "primate antigen binding portion" or a "rodent antigen binding portion," as recited in claims 39, 41, and 49. The objected-to terms have been deleted from claims 39, 41, and 49, and amended claims 39, 41, and 48 instead refer to an antigen binding portion of a primate or rodent anti-human CD23 antibody, as suggested on page 4 of the Office Action.

(2) The claims were rejected for lack of description of a method of inhibiting IgE using an anti-human CD23 antibody comprising any human gamma constant region, as recited in original claims 48-54. As amended, all of the claims are directed to an anti-human CD23 antibody having a human gamma-1 constant region.

(3) To the extent that the rejection questions whether there is support in the specification for a method wherein parenteral administration includes subcutaneous, intravenous, rectal,

vaginal and intraperitoneal administration, as recited in claim original 52, and wherein the antibody is lyophilized for storage and reconstituted prior to administration as recited in original claim 54, support for the claimed subject matter is found in the specification, for example, in lines 10-15 of page 85, and in lines 19-24 of page 94, respectively.

(4) The claims were rejected on the grounds that the specification does not describe a method using any anti-human CD23 antibodies other than antibodies having a human gamma-1 constant region and the antigen binding portions of primate antibodies 5E8 or 6G5. Applicants traverse this ground for rejection. The specification clearly states that the claimed invention can be practiced with anti-human CD23 antibodies with gamma-1 constant regions that compete with primate monoclonal antibodies 5E8 and 6G5 for binding to CD23 (page 21, lines 19-21), it discloses methods for obtaining antibodies having the CD23-binding specificities of antibodies 5E8 and 6G5, and it describes methods useful for making human and non-human anti-CD23 antibodies (e.g., on pages 19-21 and 24-26) and screening these to obtain additional antibodies that compete for binding to CD23 with primate antibodies 5E8 and 6G5 (e.g., on pages 36-41). The claims are directed to methods for inhibiting production of IgE in a human subject, and the specification describes the claimed methods and provides working examples in such terms that one skilled in the art would reasonably conclude that Applicants were in possession of the claimed invention at the time the application was filed.

(5) Claim 52 was rejected on the ground that there is no support in the specification for "intravascular" administration. The term "intravascular" has been deleted from the claims and is replaced by "intramuscular," support for which in the specification, for example, in lines 12-15 on page 85.

In view of the foregoing, Applicants respectfully request that the rejection of the claims under 35 U.S.C. 112, 1st paragraph, for lack of written description, be withdrawn.

35 U.S.C. §112, Second Paragraph

Claims 39, 41, and 49-54 were rejected under 35 U.S.C. 112, 2nd paragraph, as being indefinite because the meaning of the phrases "primate antigen binding portion" and "rodent antigen binding portion," as recited in claims 39, 41, and 49, is unclear. As noted above, the objected-to phrases have been deleted from claims 39, 41, and 49, and amended claims 39, 41, and 48 instead refer to an antigen binding portion of a primate or rodent anti-human

CD23 antibody, as suggested on page 4 of the Office Action. Withdrawal of the rejection is therefore respectfully requested.

35 U.S.C. §102(a)

Claims 38, 40-45, 47, and 49-50 were rejected under 35 U.S.C. 102(a) as being anticipated by WO 96/12741 (Bonnefoy et al.), published on 2 May 1996, as evidenced by Saxon et al. (1991). The WO 96/12741 publication is described as giving the general teaching to treat allergic disease in a human subject by administering an anti-CD23 antibody that may be a chimeric antibody having a human constant region selected from a list that includes the human gamma-1 constant region (p. 5 of the reference). The Saxon et al. is described in the office action as teaching that inhibition of IL4-induced IgE production is an inherent property of anti-CD23 antibodies. The Applicants strongly disagree with the examiner's view that Saxon et al. teaches inhibition of IL4-induced IgE production is an inherent property of any anti-CD23 antibody.

At the time the invention was made, it was well known by persons skilled in the art that different antibodies that bind specifically to a given antigen may bind to different sites (epitopes) on the antigen, and that the biological effect of binding of an antibody to an antigen is a function of the particular physical epitope on the antigen at which the antibody binds. The present application describes making cell lines that produce 5 different anti-CD23 antibodies, one of which did not inhibit Il-4-induced IgE synthesis, and two of which did not compete for binding to CD23 with 5E8, and did not inhibit Il-4-induced IgE synthesis as effectively as 5E8 and 6G5 (see p. 41). These results clearly demonstrate that different antibodies can bind specifically to different epitopes on the CD23 antigen, and that the biological effect of the binding of an antibody to CD23 depends on the particular epitope at which the antibody binds. Bonnefoy et al. (Eur J. Immunol., 1990, 20:139-144) describe assays showing that different anti-CD23 antibodies to bind to different epitopes on CD23, and that only a subset of anti-CD23 antibodies inhibit IL-4 induced IgE synthesis (see entire article; copy attached). Saxon et al. describes results obtained with two specific rodent monoclonal antibodies, mAb135 and mAb45, obtained from Dr. Guy Delespesse (see p. 4001, top left). In view of the foregoing, the applicants submit that at the time the application was filed, persons of ordinary skill in the art would have recognized that the biological effects

of binding to CD23 of any antibodies other than mAb135 and mAb45 could not be reliably predicted from the results reported in Saxon et al.

As amended, all of the claims are directed to methods comprising administering a therapeutic amount of a monoclonal anti-CD23 antibody to a human subject with an IgE-mediated allergic disorder, wherein the anti-CD23 antibody comprises a human gamma-1 constant region and competes for binding to CD23 with an antibody having the CDRs of antibody 5E8 or antibody 6G5. The cited WO 96/12741 publication does not describe or suggest making and using anti-CD23 antibodies having a human gamma-1 constant region that compete for binding to CD23 with an antibody having the specificity of primate antibodies 5E8 and 6G5. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently, described, in a single prior art reference." Verdegaal Bros. v. Union Oil Co. of California, 814 F.2d 628, 631 (Fed. Cir. 1987, cited in M.P.E.P., § 2131). Applicants submit that the claimed invention is neither expressly nor inherently disclosed by the cited references.

> "To serve as an anticipation when the reference is silent about the asserted inherent characteristic, such gap in the reference may be filled with recourse to extrinsic evidence. Such evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. In re Oelrich, 666 F.2d 578, 581, 212 U.S.P.Q. 323, 326 (CCPA 1981) (quoting Hansgirg v Kemmer, 102 F.2d 212, 214, 40 U.S.P.Q. 665, 667 (CCPA 1939) provides: Inherency, however may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient [citations omitted]. If, however, the disclosure is sufficient to show that the natural result flowing from the operation as taught would result in the performance of the questioned function, it seems to be well settled that the disclosure should be regarded as sufficient. This modest flexibility in the rule that "anticipation" requires that every element of the claims appear in a single reference accommodates situations where the common knowledge of technologists is not recorded in the reference; that is where technological facts are known to those in the field of the invention, albeit not known to judges."

Continental Can Co. v. Monsanto Co., 948 F.2d 1264, 20 U.S.P.Q.2d 1746 (Fed Cir. 1991, cited in M.P.E.P., § 2131.01(III)). At the time the application was filed, it was not common knowledge of persons skilled in the art, beyond mere possibility or probability, that anti-CD23 antibodies that compete for binding to CD23 with antibody 5E8 or antibody 6G5 could or should be obtained, that chimeric antibodies comprising the CDRs or complete variable regions of such antibodies and a human gamma-1 constant region should be produced, and that such chimeric antibodies would be operable use in the method described in the WO 96/12741 publication.

Given that the cited reference neither expressly nor inherently described or suggested practicing the claimed methods using anti-CD23 antibodies having a human gamma-1 constant region that compete for binding to CD23 with an antibody having the CDRs of antibody 5E8 or antibody 6G5, the present claims were not anticipated by the cited reference. Withdrawal of the rejection of the claims under 35 U.S.C. 102(a) is therefore respectfully requested.

35 U.S.C. §103(a)

Claims 38-39, 43-49, and 51-54 were also rejected under 35 U.S.C. 103(a) as being obvious over the publication of WO 96/12741 (Bonnefoy et al.), in view of Saxon et al. (1991) and U.S. Patent No. 5,658,570 (Newman et al.; "the '570 patent").

As discussed above, the WO 96/12741 publication did not describe or suggest practicing the claimed methods using anti-CD23 antibodies having a human gamma-1 constant region that compete for binding to CD23 with an antibody having the CDRs of antibody 5E8 or antibody 6G5. The teachings of the Saxon et al. reference would not have remedied the deficiency in the teachings of the WO 96/12741 publication, for the reasons discussed above. Nor would this deficiency have been remedied by the disclosure of the '570 patent, which describes a method for making Primatized® antibodies. At the time the application was filed, persons of ordinary skill in the art recognized that there are multiple epitopes on CD23 to which antibodies can bind to effect IgE inhibition (see Bettler et al., PNAS 86:7118-22, 1989, copy attached), and that there are multiple different classes of human immunoglobulin constant regions that could be used to make an anti-CD23 antibody having a human constant region as described the WO 96/12741 publication. The selection from all of these possibilities of an antibody comprising the particular combination of a

human gamma-1 constant region and the variable regions of an antibody that competes for binding to CD23 with an antibody having the CDRs of antibody 5E8 or antibody 6G5, as directed by the present claims, could only have been made through hindsight. It is improper to use the Applicants' own teaching as the basis for selecting the combination of elements that make up the claimed invention, in order to establish obviousness under 35 U.S.C. 103(a).

Given that the prior art references did not describe or suggest the claimed invention so that a person of ordinary skill in the art would have been motivated to select the claimed combination and practice the claimed method with a reasonable likelihood of success, the Applicants submit that the claimed invention was not obvious in view of the cited references, and respectfully request that the rejection of the claims under 35 U.S.C. 103(a) in view of the prior art be withdrawn.

## Conclusion

All rejections having been addressed, it is respectfully submitted that the present application is in condition for allowance and a Notice to that effect is earnestly solicited. If any points remain in issue, which the examiner feels may be best resolved through a personal or telephone interview, he is kindly requested to contact the undersigned attorney at the telephone number listed below.

Respectfully submitted,

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**Attachments:**

Copies of

(a) Bonnefoy et al., Eur J. Immunol., 20:139-144, 1990.

(b) Bettler et al., PNAS, 86:7118-22, 1989.

and Form PTO-1449 citing the same.